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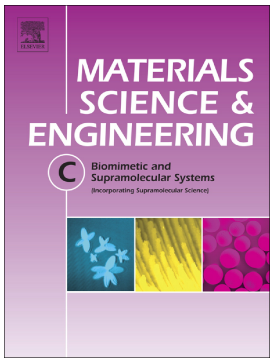

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Effect of melt extrudability and melt binding efficiency of polyvinyl caprolactam polyvinyl acetate polyethylene glycol graft copolymer (Soluplus®) on release pattern of hydrophilic and high dose drugs

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Effect of melt extrudability and melt binding efficiency of polyvinyl caprolactam polyvinyl acetate polyethylene glycol graft copolymer (Soluplus®) on release pattern of hydrophilic and high dose drugs

Abstract:

The present study explores the effect of melt binding of Soluplus® on *in vitro* release profiles of two hydrophilic drugs, metformin hydrochloride, and paracetamol. The melt viscosities of bulk polymer and physical mixtures with different concentrations of selected APIs were analyzed by using a rheometer. The rheological evaluation revealed both the suitable temperature range for melt extrusion process and drug-polymer extrudability. The effect of formulation and processing parameters (e.g. polymer/drug ratio, temperature, screw speed) on extrudability were evaluated in terms of torque and residence time analysis. The extrudates obtained via hot melt extrusion (HME) processing exhibited good flow and compressibility. Differential scanning calorimetry (DSC) and X-ray diffraction studies examined the change in glass transition temperature (Tg) and crystalline pattern of extruded formulations where all extruded formulations seemed to have retained their crystallinity. The thermogravimetric analysis determined the thermal stability (weight loss) as a function of operating temperature whereas scanning electron microscopy (SEM) showed agglomerated microstructure and rough surface with a porous network and void spaces. The tablets obtained after compression of milled extrudates showed excellent hardness with robust tablet characteristics. The *in vitro* release studies of individual batches performed in various USP recommended dissolution media (for paracetamol) showed the pH-independent release of the hydrophilic drugs from the polymer matrices.

Keywords: Melt binding, extrudability, Hydrophilic drugs, Soluplus®, drug release.

1. Introduction

Hot melt extrusion (HME) has recently appeared as an emerging technology in the pharmaceutical industry to develop and manufacture various drug delivery systems and is set to influence the research and development in the pharmaceutical field [1]. It involves the application of temperature and high shear to formulate molecular dispersion of polymer and drug substances. HME provides solvent and dust free operation with continuity in the manufacturing process as mixing, melting, granulation, shaping and conveying are performed by a single machine [2]. Many researchers claimed that HME technique can maintain high-quality demand as this technique provides flexible and efficient mixing with inline monitoring, automation and thereby reduces capital and labor cost. HME has also been used for masking the taste of bitter API [3,4], production of extrudates with modified or sustained release properties and enhanced bioavailability by controlling both formulation and processing parameters [1,5]. Hot melt extrusion has been employed to prepare various drug delivery systems, including pellets, sustained release tablet/capsule [5-8], transdermal drug delivery systems [9,10] and implants [11,12]. Various types of downstream devices can be used to get different shapes of the final product such as molded shaped or circular dies can be applied to obtain continuous extrusion which can cut the extruded products into desired size or length. Die face cutting can be applied to obtain pellets whereas film die with conveying element and roller can be used to prepare film/strip or sheet. Each shape requires a designed mold and finishing without any undercuts on the surface or inside the shaped cavity [9, 13].

A good knowledge of the material properties, such as drug-polymer miscibility, melt viscosity and glass transition temperature (Tg) of polymers is needed before the optimization of processing conditions to develop new products. The drug-polymer mixtures should also be extrudable at as low temperature as possible to minimize the potential degradation of drug, polymer or both. It should be considered that the influences of processing parameters are dependent on the physical and chemical properties of the API and the polymer used [14]. The physico-mechanical (thermal and rheological) evaluation of drug, polymer and corresponding binary mixture can provide the insight about miscibility and behavior of material during HME process which helps in the optimization and scale-up of the formulation [15]. The extruded formulation contains API incorporated in a carrier (polymer) which should deform easily and

remain stable at processing condition. Carrier/polymer in such extruded form acts as a meltable binder and release retardant [16]. Thus the polymer selection is the critical factor to get the desired drug release profile during formulation design and optimization of melt extruded product [17]. Various hydrophilic (HPMC, HPC, Carbopol) and hydrophobic (acrylates or eudragit) polymers are mostly used to retard the release pattern of highly soluble drugs and to develop extended release formulations [18-21]. However, the use of a hydrophilic polymer to control the release pattern of highly soluble drugs is somewhat difficult due to the fast diffusion of the dissolved drug from the hydrophilic gel layer [22]. Hydrophobic polymers like ethylcellulose and eudragit are considered as safe, stable and widely used in the development of sustained release formulation [23]. Besides the choice of polymer, selection of the plasticizer is a crucial formulation parameter which ultimately affects the HME processing. They are mostly used in the polymer industry to increase the flexibility of the polymer, decrease the brittleness of the product and reduce the extrusion temperature [24, 25]. The plasticizing effect can be observed by thermal analysis as a decrease in glass transition temperature (Tg), a change in melting temperature and crystalline pattern [26]. Some drugs possess the plasticizing ability by reducing the friction between the polymers and enables lowering the operating temperature, which can prevent them from thermal degradation (in the case of thermal sensitive drugs) [27,28].

Polyvinyl Caprolactam-polyvinyl acetate-polyethylene glycol (Soluplus®) is a graft copolymer with an average molecular weight 90,000 -140,000g/mol and available with trade name Soluplus® (Fig.1). It is recommended for solubilizing poorly soluble APIs due to its amphiphilic nature [29]. Due to its low hygroscopicity, glass transition temperature (Tg), and melt viscosity, it is mostly used in pharmaceutical processes such as spray drying, melt extrusion, wet granulation and direct compression [29-31]. It is capable to form micelle structure in solution and acts as a polymeric solubilizer to enhance solubility and bioavailability of poorly soluble drugs like fenofibrate, lovastatin, carbamazepine etc. [31-34]. This copolymer is also reported to act as a thickening and gelling agent as a function of temperature [35, 36]. F. Alvarez-Rivera et al., formulated alpha-Lipoic Acid polymeric nano micelles using Soluplus as solubility and corneal permeability enhancer. They also evaluated the ocular toxicity and corneal permeability at EU Reference Laboratory following US Interagency Coordinating Committee. [36,37]. J. Young et al., used Soluplus along with TPGS to prepare solid dispersion to improve the

bioavailability of valsartan by using hot melt extrusion technique designed with twin screw extruder system [38]. Similarly, J. Fan et al., applied Soluplus to prepare a ternary complex system of baicalein phospholipids and copolymer (Soluplus®) to enhance the dissolution and flowability of baicalein phospholipids complex. They also performed the *in vivo* pharmacokinetics study using male SD rats [39]. J. Hou et al. used two biocompatible copolymers, Soluplus and Solutol HS 15 to develop paclitaxel loaded mixed micelles by using solvent evaporation method to enhance solubility, bioavailability and anticancer activity of paclitaxel [40]. X. Lian et al developed amorphous solid dispersion of 9-nitrocamptothecin with Soluplus via lyophilization method and assessed oral bioavailability, gastrointestinal safety and antitumor activity [41].

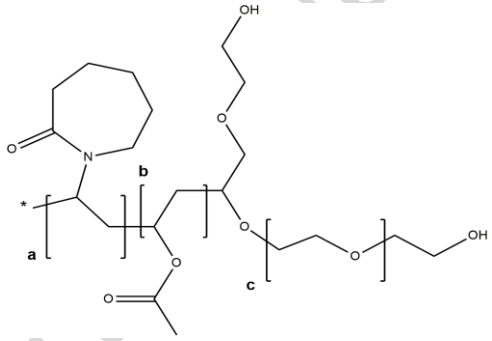

Fig. 1. Molecular structure of Soluplus®

However, majority of the reported studies utilized Soluplus® to develop solid-dispersion or to enhance the dissolution rate of the poorly water-soluble drugs. None of the studies reported the melt-binding effect of soluplus with high dose and poorly compressible hydrophilic drugs. Hence, hydrophilic metformin HCl and paracetamol were selected as model drugs to study the effect of different ratios of Soluplus® on extrudability, melt binding, processing conditions and release pattern of drugs. The extrudability of plain polymer and the drug-polymer mixture were measured from the moment of force (torque) generated onto the screws in the barrel during the melt extrusion process. It can be considered that viscosity and torque analysis would help in the optimization of processing parameters (temperature, screw speed, feed rate, etc.) during HME process and will give an idea about the miscibility of drug-polymer mixtures [14]. The

miscibility and melt binding of the drug-polymer mixtures after HME process were analyzed by differential scanning calorimetry (DSC) and X-ray diffraction analysis (XRD) studies and the results obtained were compared with that of the physical blends.

2. Materials and methods

2.1. Materials

Soluplus® (Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) was obtained as a gift sample from BASF Corporation, Mumbai India (Head office Ludwigshafen, Germany). Paracetamol was purchased from Sigma Aldrich Corp (Mumbai, India) and Metformin Hydrochloride was kindly supplied by USV Pvt Ltd (Mumbai India) as a gift sample. All reagents and chemical used were of analytical grade and were used as received.

2.2. Rheological evaluation

The rheological evaluation of plain polymer and binary mixture with APIs were carried out by analyzing the effect of shear rate and temperature on the melt viscosity in oscillation mode by using Anton Paar Physica MCR101rheometer operated by RheoPlus-32V3 software (Anton Paar Germany). The parallel plate geometry of 25 mm diameter with a gap distance of 1 mm was employed. About 2 gm of the sample placed in between the plates after calibration of the gap between the plates. The experiment was conducted at 100-180°C with an increment of 5°C and the plots of resulted viscosity versus angular frequency were obtained and responses were generated in terms of viscosity (Pa.s) versus temperature (°C). The temperature range selected in these experiments was based on the thermal characteristics of the polymer and corresponding physical mixture which was analyzed prior to the experiment by TGA and DSC. All the samples were analyzed in duplicate. Power laws equation explain rheological behavior with a shear rate which is given as follows.

$$\eta = K \gamma^{(n-1)} \quad (1)$$

Where η represent viscosity coefficient, γ indicate shear rate and n is power law index. In case of shear thinning polymers, $0<n<1$ [13, 28].

2.3. Preparation of physical blend

The dry APIs and polymer (Soluplus®) blend (250 gm) were prepared by physical mixing according to the percentage ratio given in Table 1. API content of blend varied from 80-90% in the case of metformin (MTF) while for paracetamol (PML) the drug content varied from 80 to 98%.

Table 1 Drug-polymer ratio and HME processing parameters

	Batch code	**Drug-Polymer ratio (%)**	**HME processing parameter**										
			Feed rate (Kg/hr)	**Screw speed (rpm)**	**Residence time (min)**	**Temperature (°C) of Zones from feeder to die**							
						Die	8	7	6*	5*	4	3	2
		PML: Soluplus											
1	P1	98:2	2-4	150-170	5-6	90	110	110	120	120	100	90	90
2	P2	97:3	2-4	160-170	5-6	90	100	110	120	120	100	90	90
3	P3	96:4	2-4	160-170	5-6	90	100	110	120	120	90	90	85
4	P4	95:5	2-4	150-160	5-6	90	90	100	110	110	90	85	80
5	P5	92:8	2-4	140-150	7-8	80	85	90	100	100	90	85	80
6	P6	90:10	2-4	140-150	7-8	80	85	85	90	90	85	85	80
7	P7	85:15	2-4	140-150	7-8	70	80	80	85	85	80	80	80
8	P8	80:20	2-4	140-150	7-8	70	80	80	85	85	80	80	80
		MTF: Soluplus											
9	M1	93:7	1-2	90-100	8-9	120	130	130	140	140	130	130	130
10	M2	90:10	1-2	90-100	8-9	110	120	120	130	130	120	120	120
11	M3	85:15	1-2	80-90	8-9	110	120	120	125	125	110	110	100
12	M4	80:20	1-2	80-90	7-8	100	110	110	120	120	110	110	100
13	M5	75:25	1-2	80-90	7-8	90	100	100	110	110	100	100	100

* Indicating kneading zones.

2.4. HME Process

Twin screw extruder (23.5 mm diameter and 1059 mm shaft length) system was used for extrusion processing made by ACG Pharma Ltd, Pune India, equipped with a gravimetric feeder (Coperion k-TRON Germany) a standard die having size 2.5 mm was selected for uniform extrude which was pre-evaluated for the extrusion process. The blend mixtures of APIs and polymer were poured into the hopper of the feeder which passes on the rotating screws with a constant feeding rate (2-4 kg/hr for Paracetamol and 1-2 kg/hr for Metformin) the screw temperatures and speed varied with respect to the polymer ratio for both APIs which ultimately affect on residence time as shown in Table 1.

2.5. Particle size analysis

The PML and MTF melt extruded granules' particle size distributions were measured by sieve analysis using electromagnetic sieve shaker (Electrolab India Pvt. Ltd.). Approximately, 50 g of granules were placed on the top sieve of the stacked-sieves and then the nest of the arranged sieves was subject to agitation for 20 min. The weight of the granules retained on each sieve was accurately calculated to get weight percentage of granules in each sieve size range. The experiment was conducted in triplicate and the mean was calculated.

2.6. Determination of granule strength

The granules strength was determined by performing repeated impact test (RIT) to check the breaking nature of the granules. The test involves inflicting the granules to the fatigue in a sample holder which vibrates at a specified frequency and amplitude with a unidirectional movement which causes reproducible damage to the granules. A granules sample of the size range between 200-300 µm (pre-sieved) were placed in the sample holder and subjected to resonance at 50 Hz and 100 collisions with wall per second with regulated impact velocity and amplitude. The test was performed in triplicate and the fraction fractured or damaged during the test was passed through the sieve and calculated as mean using formula given as follows [42, 43, 44].

$$Wd = \frac{Wi - Wr}{Wi}$$

Where,

Wd= Damaged fraction, *Wi*= Initial weight of sample and *Wr*= weight retained.

2.7. Friability of granules

The granules friability was determined using friabilator (Abrasion drum-EF 2W Electrolab India Pvt. Ltd.) 10 g of granule samples retaining on 250 µm size mesh was put to friabilator and rotated at 25 rpm for 20 min. The resultant granules samples were sieved from 250 µm and the fraction retained on the sieve was weighted and the percentage friability of granules (F*g*) was calculated using the following equation.

$$F_g = W_i - W_f / Wi * 100$$

Where W_i is initial weight and W_f is the final weight of the granules after sieving.

2.8. Tablet preparation

The extrudes obtained after HME process was passed through the mesh with an aperture size 400µm, and the blends were compressed to a tablet by using Cadmach compression machine Ahmedabad India, the dose of the paracetamol and Metformin was kept constant (i.e. 500 mg).

2.9. Characterization

2.9.1. Differential Scanning Calorimetry

The physical state of Pure APIs and extruded materials were studied by Differential Scanning Calorimetry using Perkin Elmer differential scanning calorimeter equipped with Pyris manager software (Shelton USA). Approximately 3-4 mg of sample was hermetically sealed in an aluminum pan and heated from 30° - 300°C at the rate of 10°C /min under an inert atmosphere maintained by purging nitrogen gas at a flow rate of 18-20 ml/min.

2.9.2. Fourier Transform Infrared (FTIR) Spectroscopy

Fourier transform-infrared spectroscopy (FT-IR) spectra were obtained by using Perkin Elmer FTIR (Spectrum Two L160000A) spectrometer. Pellets of all the samples were prepared by mixing samples with an appropriate quantity of potassium bromide. Pellets were compressed using a hydraulic press by applying 10-12N compression force. The spectra were recorded over a scanning range of 400-4000 cm^{-1}.

2.9.3. X-ray diffraction Analysis

X-ray powder diffraction technique was used to assess the crystalline state of the pure drug and extruded formulations, all the samples, including APIs and extruded formulation were analyzed by using X-ray diffraction apparatus (Bruker D8 Advance USA) in a theta-theta mode using the Cu x-ray tube and xenon detector at 40 kV with 20 MA current. The samples were scanned from 5 to 65° 2-theta at a scanning speed of 2.0 degree/min.

2.9.4. Drug loading determination

For quantification of the paracetamol and metformin HCl, 20 tablets of each formulation were weighed and powdered. A crushed powder equivalent to 100 mg of paracetamol was weighed, dissolved in methanol in a 100 ml volumetric flask and sonicated for 10 min. After appropriate dilution with water, measurement was done at 243 nm spectrophotometrically. Similarly, powder equivalent to 100 mg of metformin HCl was weighed and dissolved in 100 ml purified water, filtered and diluted to get a final concentration of 10 µg/ml and absorbance was measured at 232 nm.

2.9.5. In-vitro dissolution studies

Dissolution studies for all formulations carried out as per USP recommendation, for paracetamol tablets 900ml of pH 5.8 phosphate buffer and simulated gastric fluid TS (without enzyme) media were used while pH 6.8 phosphate buffer was used for Metformin tablets. The in vitro studies were carried out by using USP II paddle type dissolution apparatus (Electrolab Mumbai, India) at 50 rpm (for paracetamol) and 75 rpm (for Metformin) maintaining temperature 37 ± 0.5°C. Samples were drawn from each vessel at different time intervals filtered using a 0.45µm filter and analyzed by a UV spectrophotometer (Shimadzu UV-1800) at 243 nm and 233 nm respectively. The withdrawn sample from the vessel was immediately replaced by an equal volume of fresh buffer. The dissolution study was performed in triplicate. The cumulative percentage of drug release was calculated and plotted against time.

2.9.6. Scanning electron microscopy

The surface morphology and shape of plain APIs and extruded formulation were examined by means of scanning electron microscope (Jeol JSM 6380LA Japan) operated at 20-25 kV voltage,

the samples were fixed on the glass stub with a double-sided adhesive tape and coated with platinum by using Autofine couture (JEOL JFC 1600) and then studied under electron microscope.

2.9.7. Thermo Gravimetric Analysis (TGA)

The thermal stability of plain APIs, polymer, physical mixture, and extruded formulation were determined as a function of weight loss, the analysis was carried out with approximate 6-8 mg of the sample by using Shimadzu DTG 60H thermogravimetric analyzer in the temperature range from 25-300 °C with a heating rate of 10 °C/min. The analysis was carried out under the continue nitrogen flow of 50 ml/min. The percent weight loss of all the samples was recorded with respect to temperature by using TA60 WS thermal analysis software (Shimadzu Japan).

2.10. Statistical analysis

All experiments were performed in triplicates and the data were expressed in terms of mean ± Standard deviation using SPSS Statistics® (IBM) software and a Student's *t*-test was used to analyze the results. A $p<0.05$ was considered as statistically significant.

3. Results and Discussion

3.1. Rheology

The rheological analysis was performed to determine the melt viscosity and influence of the addition of APIs on the melt viscosity of the polymer at a different temperature. The objective of this study was to predict the process and formulation parameter during the HME process such as processing temperature, the plasticizing effect of drug and drug/polymer miscibility. The viscosity of bulk Soluplus® was <70,000 Pa.s at an initial temperature of 105°C and it gradually decreased with the increase in the applied temperature. The viscosity dropped below 10,000 Pa. s when temperature increased over 170°C. As expected, owing to the nature of the crystalline drugs, the addition of APIs with increasing concentration of 10%, 25% and 50% by weight caused a decrease in the viscosity values observed at all temperature (Fig.2). The binary mixture containing 50:50 drug/polymer ratio showed viscosity around 25000 Pa.s at 105°C and it dropped below 1000 Pa.s above 180°C. The viscosity values at 100 to 140 °C were 25500 to 5000 Pa.s which indicated that this temperature range will be suitable for melt extrusion process to get the

well-extruded material. The melt viscosity of plain Soluplus® and binary mixture with APIs showed shear thinning behavior since it decreased as the angular frequency or shear rate increased (followed power law equation) and melt viscosity was temperature dependent, as plain Soluplus® as well as all binary mixtures exhibited a decrease in viscosity with an increase in temperature.

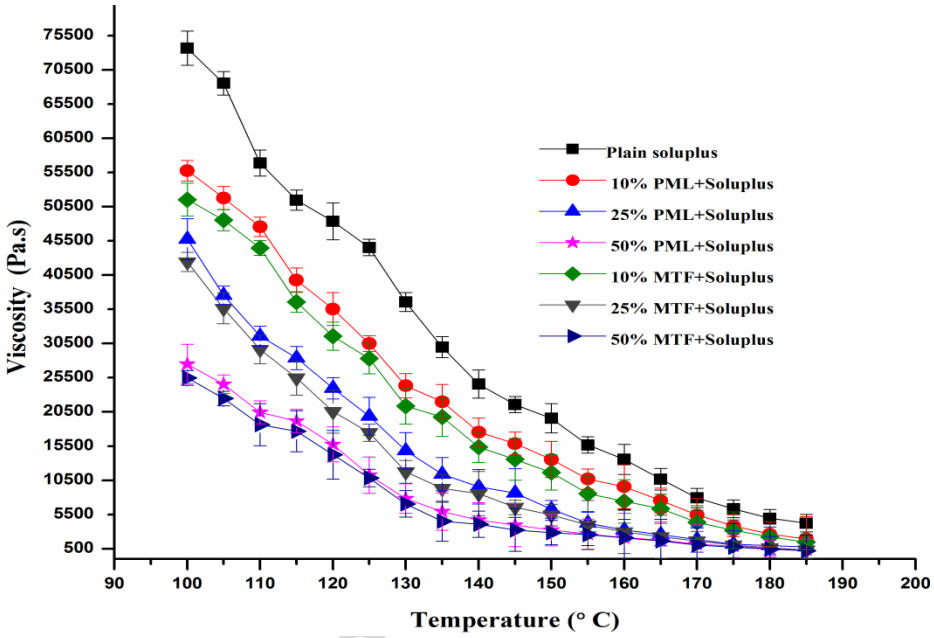

Fig. 2. Rheological analysis of Soluplus® and physical mixture with a different concentration of APIs, Mean values ± S.D. (n=3).

3.2. HME processing and optimization

It was observed that as the concentration of Soluplus® increases the viscoelastic effect and extrudability increases while operating temperature decreases. The temperature range which gives the melting of the polymer or API polymer mixture could be determined by comparing with a torque value generated during melt extrusion (ME) process as torque varies according to viscoelastic properties of materials. The influence of temperature on torque value during the ME process is shown in Fig.3a. In ME of paracetamol (PML) and metformin (MTF), the drug content varied from 80-98% and 75-93%, respectively while Soluplus® concentration varied from 2-25%. As the percentage ratio of drug increases, the processing temperature of barrel increases to melt the Soluplus® from the bulk API, but when the temperature was kept constant or decreased,

there was an increase in the % torque value which reflects the stiffness of the material at kneading zone of the barrel (Fig.3b).

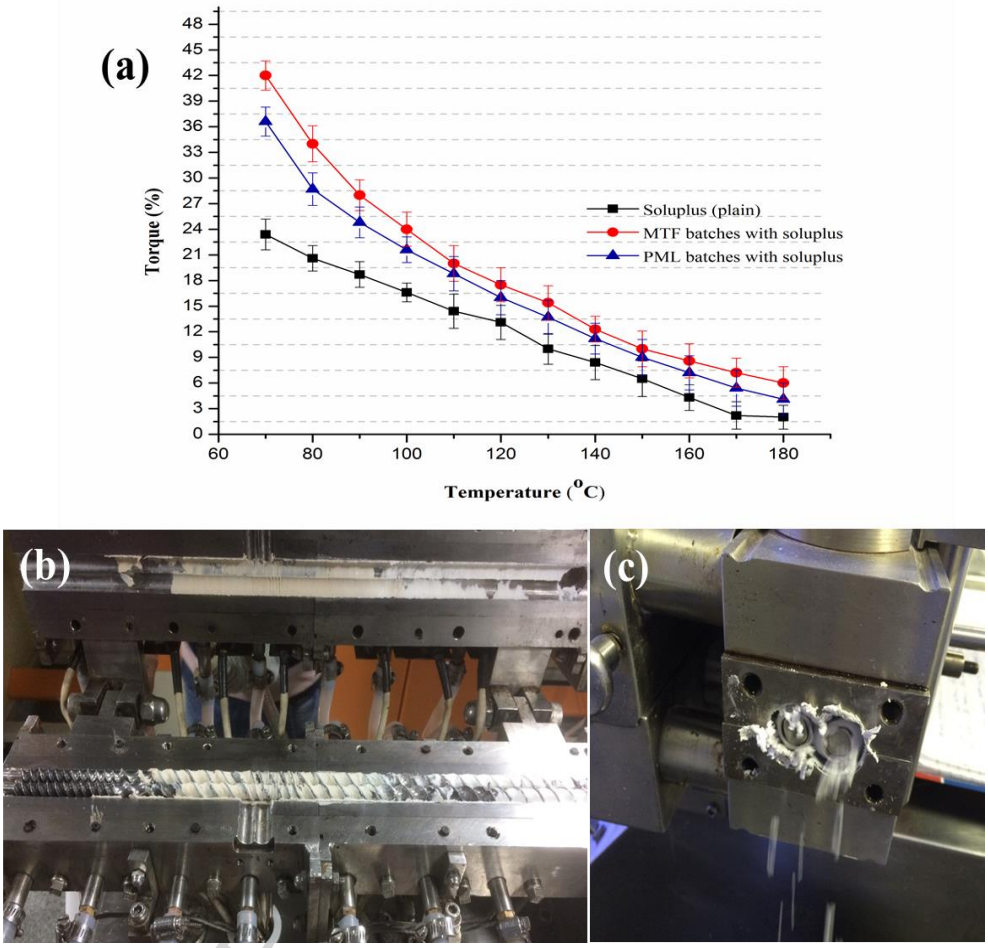

Fig. 3. (a) Effect of processing temperature on torque parameter, (b) stiffness of material at Kneading zone below 80 °C (Torque 40-42%), (c) well-extruded material at optimized temperature. Mean values ± S.D. (n=3).

The processing temperature for PML and MTF batches were optimized between 80-120°C and 90-140°C as per drug-polymer ratios whereas the torque value was observed between 15-20% (Fig.3c). A slight decrease in the temperature value below 80°C increased the torque parameter up to 42%. Similarly, screw speed played an important role in the extrudability of the drug-polymer mixture. With the increase in the API concentration, the screw speed had to be increased in order to minimize the residence time and prevent the material from charring during ME process. The increase in screw rotation speed will cause two phenomena: (i) generation of high shearing stress on material for better distribution of drug with the polymer matrix which

improves viscoelastic properties, and (ii) reduce the residence time (Rt) of material [45-49]. During the ME process of PML: SOL and MTF: SOL blends, the screw speed was optimized in between 90-170 rpm. The screw speed range for PML batches (P1, P2, P3, P4, P5, P6, P7 and P8) was optimized at 140-170 rpm (in accordance with the API: polymer ratio, the screw speed varied such as batches PI P2 and P3 processed at 160-170 rpm, P4 at 150-160 rpm and P5, P6, P7 & P8 extruded at 140-150 rpm) and the Rt was 5-6 min. Interestingly, for the same batches when the screw speed decreased below 140 rpm the Rt elevated up to 10 min. Similarly, for MTF batches (M1, M2, M3, M4, and M5) processed at screw speed range 80-100 rpm the Rt was observed around 8-9 min and a decrease in screw speed below 80 rpm caused an elevation in Rt up to 20 min.

The particle size analysis of the melt extruded granules of PML and MTF is depicted in Fig.4. The PML granules exhibited broad particle size distribution of the size range between 80-100 µm with a low percentage of fine particle (>10%). A small fraction around 10% was found in between 420-850 µm. The majority of the granules was found in the size range between 200-420 µm. In case of MTF extruded granules, a little variation in size range was observed with the similar polymer concentration. Granules with 10% Soluplus content exhibited particle size 120-180 µm (>40%) and around 20% particles with 8-120 µm size range and 10% granules with a size range of 250-420 µm. Similarly, granules formulated with 20% Soluplus exhibited broad particle size distribution as 30-40% particles lay in the size range of 120-250 µm. Around 10% particles observed in 250-420 µm and a very small fraction was found in the range of 420-850 µm size range. The granules of both the APIs (PML and MTF) prepared by hot melt extrusion exhibited broad particle size distribution and different granular strength.

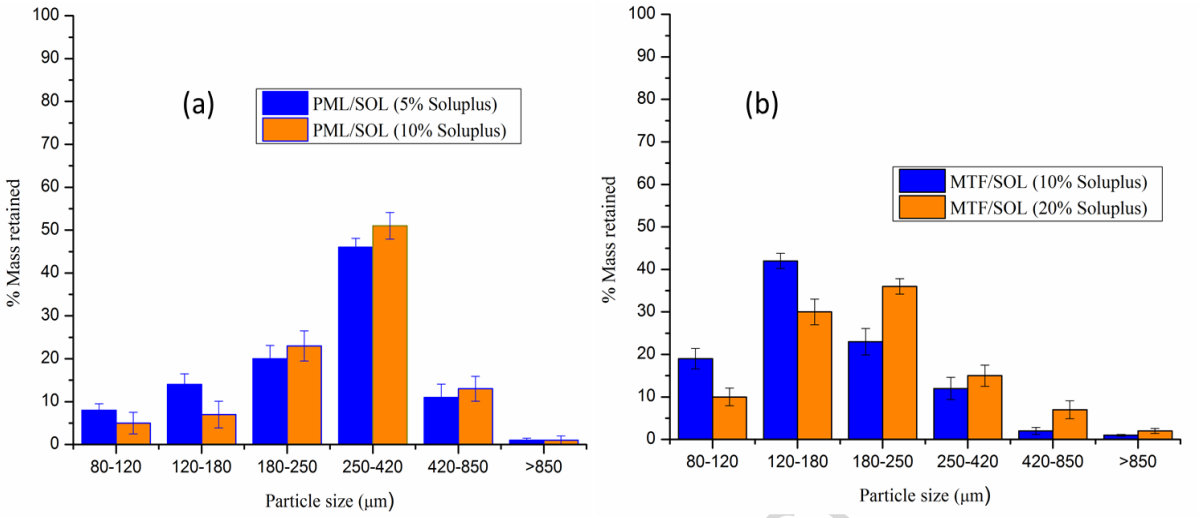

Fig.4. Particle size analysis of melt extruded granules (a) PML (b) MTF, Mean values ± SD (n=3).

The repeated impact test (RIT) was performed to evaluate the strength or toughness of the melt extruded granules and binding efficiency of Soluplus® with PML and MTF. The granules were subject to repeated impact for the time period of 10, 30, 45, 60, 90, 120, 150, 180, 210, 240 s and the damaged fraction was plotted against the number of collisions. The damage or breakage of the granules occurs by a different mechanism like fragmentation, attrition, abrasion, chipping etc. and these damages of particles depend upon the forces applied and the nature of the granules. [43]. It was observed that breakage of the particles increases as the number of collision increases (Fig.5). For PML melt extruded granules, batches P1 and P2 (2-3% SOL) showed around 50% damage rate on 24000 collision (240 s) and batches P3, P4 and P5 (4-8% SOL) exhibited 35-40% damaged fraction while for batches P6, P7, and P8 (10-20% SOL) the rate of damage is very less (<30%). Similarly, MTF melt extruded granules, the damage rate is more in case of batches M1 and M2 (45-50%) while batches M3, M4 and M5 (15-25% SOL) showed less than 40% damaged fraction. Both PML and MTF melt granules batches revealed that the Soluplus® concentration played an important role in melt binding and strength of granules, as the damaged fraction decreases with the increase in the SOL content in the formulations.

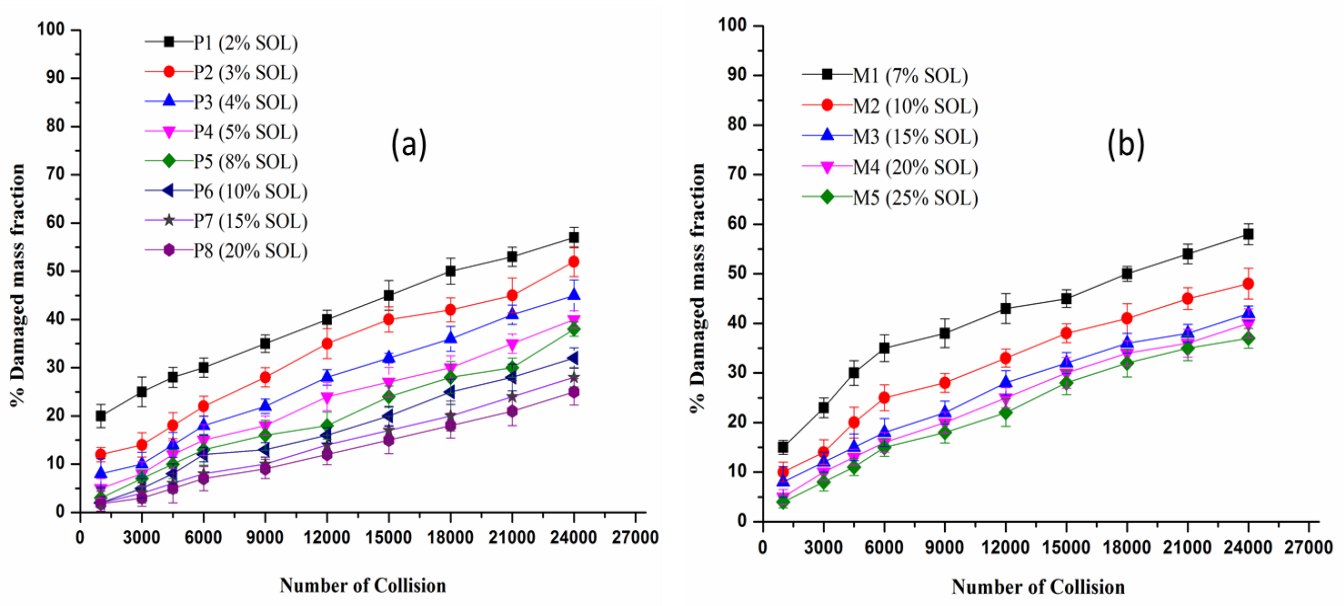

Fig. 5. Granules strength analysis (Damaged fraction Vs Number of collisions) of (a) PML extruded granules (b) MTF extruded granules, Mean values± SD (n=3).

Granules friability is indicative of the granules strength. The results for friability measurements were exhibited in Fig.6. For both the API, granules friability was low (8-24%), most friable granules was observed in formulation P1 (PML) and M1 (MTF) with mass loss of around 20-23%. This might be due to poor binding of granules owing to low soluplus® content. It was observed that friability of melt extruded granules decreases as soluplus® content in the extruded granules increases. The other factors affecting on the granules strength are screw element and temperature of the barrel. Most friable granules were observed in case of conveying elements while increasing kneading elements caused high densification and improved mixing in barrel zones resulting in less friable granules. The barrel temperature also plays an important role granules strength as it helps in melting and binding of polymer with APIs.

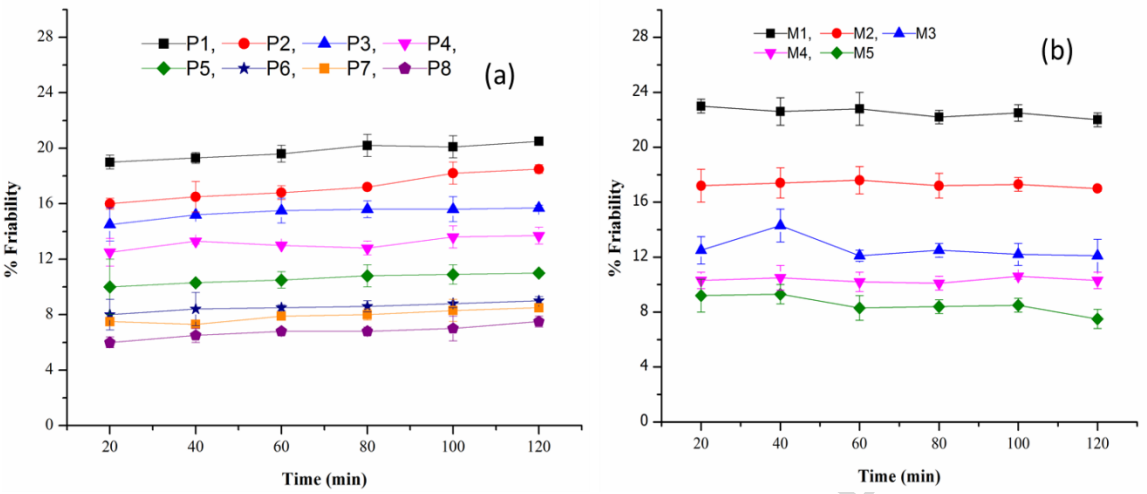

Fig.6. Friability of melt extruded granule (a) PML, (b) MTF batches (n=3, mean ±SD)

3.3. Differential Scanning Calorimetry

Differential scanning calorimetry studies of the bulk API, drug-polymer physical mixture and extruded formulations were performed and obtained thermograms are shown in Fig.7a. The thermograms of plain PML showed an endothermic peak at 172.17°C (ΔH = 56.57 J/g) corresponding to its melting point. Similarly the PML: polymer physical mixture and extruded formulations (P1, P2, P3, P4, P5, P6, P7, and P8) showed the melting peaks between 168-171°C with ΔH value 38-49 J/g with intense and similar peak of bulk PML which confirms that crystallinity of the drug was retained even after melt extrusion process. The thermogram of pure MTF extruded batches with Soluplus® and corresponding physical mixture is presented in Fig.7b. The thermal graph of pure MTF and physical mixture showed endothermic peaks at 238.5 °C (ΔH=-115.3 J/g) and 237.12°C, respectively while extruded batches (M1, M2, M3, M4, and M5) showed a melting peak at 236.8 °C, 237.6 °C, 234.6 °C, 234.1 °C and 236.7 °C respectively. These endotherms correspond to the melting peaks of the bulk drug. It can be concluded from the thermal analysis study the crystallinity of the batches did not change after the extrusion process.

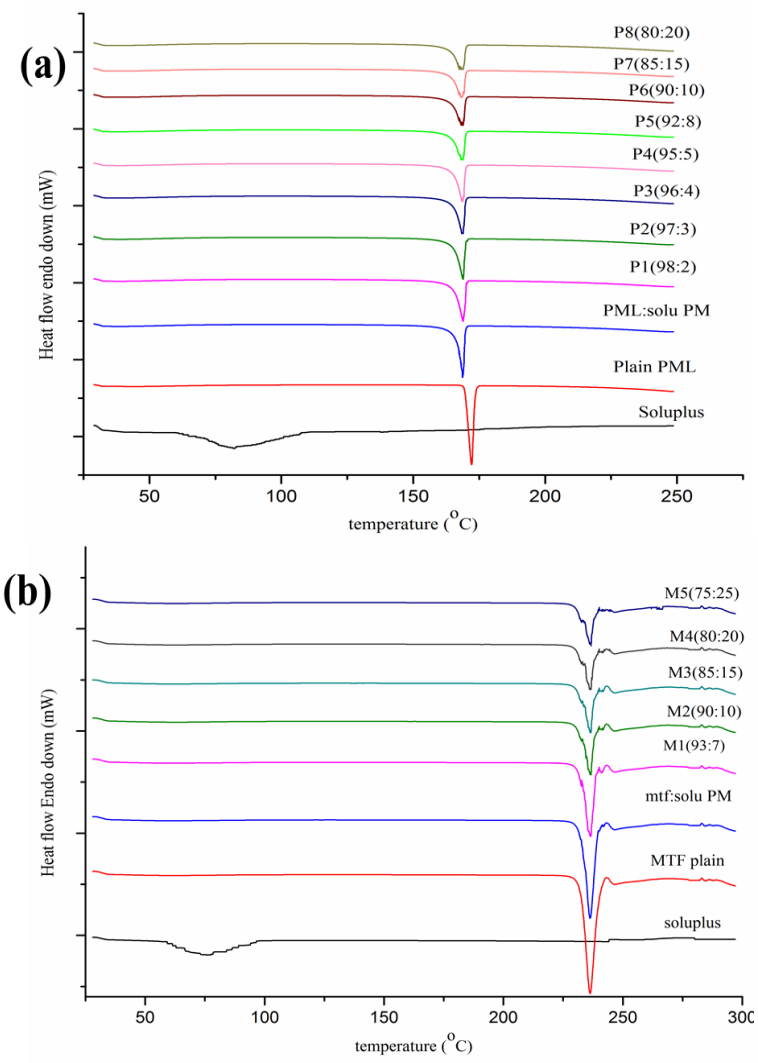

Fig. 7. DSC thermogram of (a) Plain paracetamol, Soluplus®, physical mixture and extruded batches, (b) plain Metformin HCl, physical mixture and extruded batches.

3.4. FTIR Analysis

The FTIR spectra of PML (Fig.8a) demonstrated the sharp singlet peak at 3325.1 cm^{-1} indicating -NH stretch while 3257.7 cm^{-1} band is due to O-H stretch. The aromatic stretching was observed at 3161cm^{-1} whereas the band at 1610.5 cm^{-1} is due to C=C stretching of the aromatic ring. The band at 1654 cm^{-1} is due to C=O stretch of acetanilide, bands at 2879 cm^{-1} and 1440 cm^{-1} are due to C-H stretch of alkane and -CH_3 bending vibrations, respectively. The spectra of a physical mixture of drug/polymer and extruded formulation of PML with Soluplus® showed similar peaks as that of the bulk API. The spectra didn't show any significant shifting of the peaks which

indicates the absence of any chemical interaction between PML and Soluplus® even after the ME process.

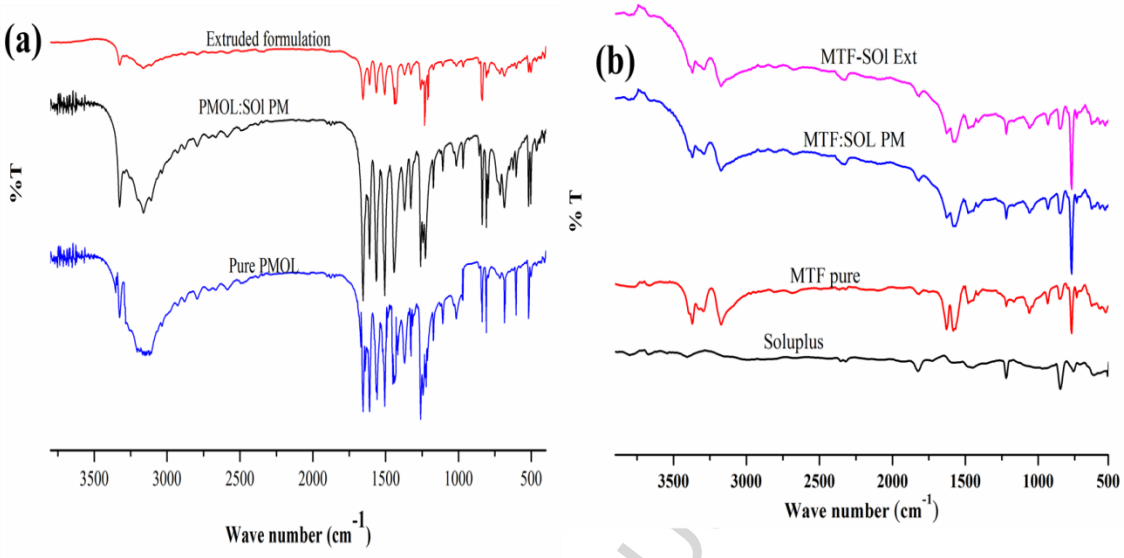

Fig.8. FT-IR spectra of (a) paracetamol, physical mixture, and extrudates, (b) Metformin HCl, Soluplus®, physical mixtures, and extrudates

The FTIR spectra of MTF (Fig.8 b) showed the selective stretching vibration at 3371 cm^{-1} and 3174 cm^{-1} for primary and secondary amines, respectively. The $-CH_3$ bending was observed at 1473 cm^{-1} whereas the band at 1627 cm^{-1} is due to C=N of imines, and at 1219cm^{-1} is due to C-N stretching of amines. The spectra of Soluplus® demonstrated the absorption band at 1734 cm^{-1} as well as the characteristic peak of ester (C=O, C-O) at 1734cm^{-1} and 1365 cm^{-1}, respectively. The stretching vibrations at 1642 cm^{-1} are due to lactam ring present and the vibration at 3569 cm^{-1} was for O-H stretching while the band at 1265 cm^{-1} was due to C-O stretch. The Spectra of a physical mixture of MTF/polymer and extruded formulation did not show any shift of peak and interaction between drug and polymer used in the formulation. This concludes that there was no chemical interaction observed after the ME process with either of the drugs.

3.5. X-ray diffraction Analysis

The x-ray diffraction studies of all the APIs, physical mixtures and extruded formulations were performed to examine the crystalline state of the drug within the extruded granules. The x-ray diffraction pattern of pure PML (Fig. 9a) exhibited a distinct and highly intense peak at 2θ

degrees positions of 12.3°, 13.1°, 15.2°, 18.2°, 20.5°, 23.8°, 24.6°, and 27.1° which indicates the crystalline nature of PML.

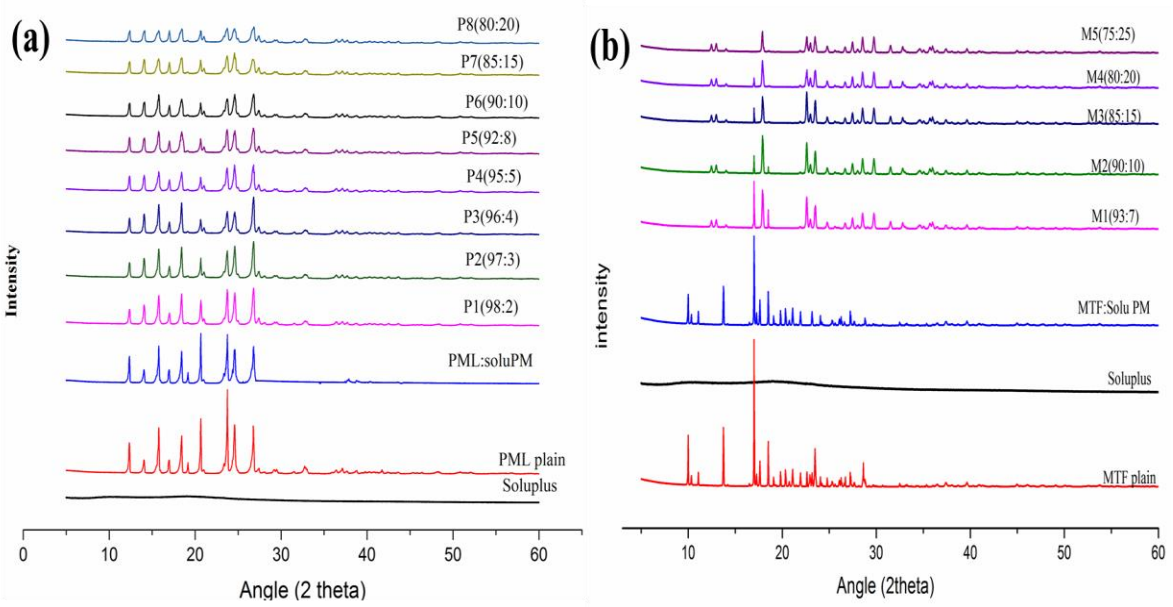

Fig.9. X-ray diffraction pattern of (a) paracetamol, Soluplus®, physical mixture, and melt extruded batches, (b) Metformin HCl, Soluplus, physical mixture and melt extruded batches.

The XRD pattern of physical mixture and extruded batches showed characteristic peaks corresponding to the pure PML but at relatively low intensities, which indicates the presence of crystalline PML in the extruded granules prepared by HME. The diffraction pattern of processed batches confirmed the Form I state of PML within the extruded granules which is a stable form of PML and no new crystalline peak were observed at any 2θ values within the scale the samples were examined via XRD [39]. XRD patterns of plain MTF (Fig. 9b) showed a distinct and intense peak at 2θ values 10.1°, 14.8°, 16.5°, 17.1°, 18.5°, 19.1°, 20.4°, 21.2°, 22.6°, 24.6° and 28.4° exhibiting the crystalline nature of the drug. However, the XRD pattern of physical mixture and extruded batches showed identical, but slightly low intense peak compared to pure MTF. It was observed that as the ratio of Soluplus® in the blend increases the intensity of peak decreases, which indicates the dispersion of the drug in the polymer.

3.6. In-vitro release studies

The *in-vitro* studies were performed for all extruded batches compressed into tablet form. The release patterns were analyzed in terms of polymer/drug ratio. From Fig. 10a, it was observed

that high drug-loaded bathes of PML such as P1, P2, P3, P4, and P5 showed a higher dissolution rate with more than 80% drug released within 60 min whereas the batches P6, P7, and P8 (Fig. 10b) with increased polymer contents (10-20% w/w) showed sustained release behavior. Batches P6 and P7 (drug loading 80-90%) showed 65-70% drug release in 60 min while batch P8 where drug loading was 80% showed only 47% drug release in 60 min. The higher concentration of polymer (Soluplus®) produces gelling in dissolution media and thereby slowed the drug release from melting extruded formulation (compressed tablet) [18]. The release pattern of batches P6, P7 and P8 were also studied in simulated gastric fluid TS (without enzyme USP 30 NF-25). It exhibited that the release profile of PML batches in SGF (Fig. 10c) showed similar dissolution behavior as in phosphate buffer (pH 5.8) which outlines that there was no significant difference in release pattern observed due to change in pH or dissolution media. The *in vitro* dissolution profiles of MTF batches were shown in Fig. 10d. It can be observed that batches M1, M2 and M3 exhibited more than 80% drug release in 45 min due to high drug loading (93%, 90%, and 85% w/w) and high hydrophilic nature of MTF. In contrast, the formulation M4 and M5 with drug loading 80% and 75% w/w showed sustained release behavior but at a much lower rate. Formulation M4 where polymer concentration was 20% w/w showed 68% drug release at 60 min whereas formulation M5 with 25% w/w polymer content exhibited 48% drug release at 60 min. The drug release patterns were greatly influenced by the amount of Soluplus® as well as the nature of the drug. The higher amount of Soluplus® reduces the erosion by gel formation and retard the drug release rate.

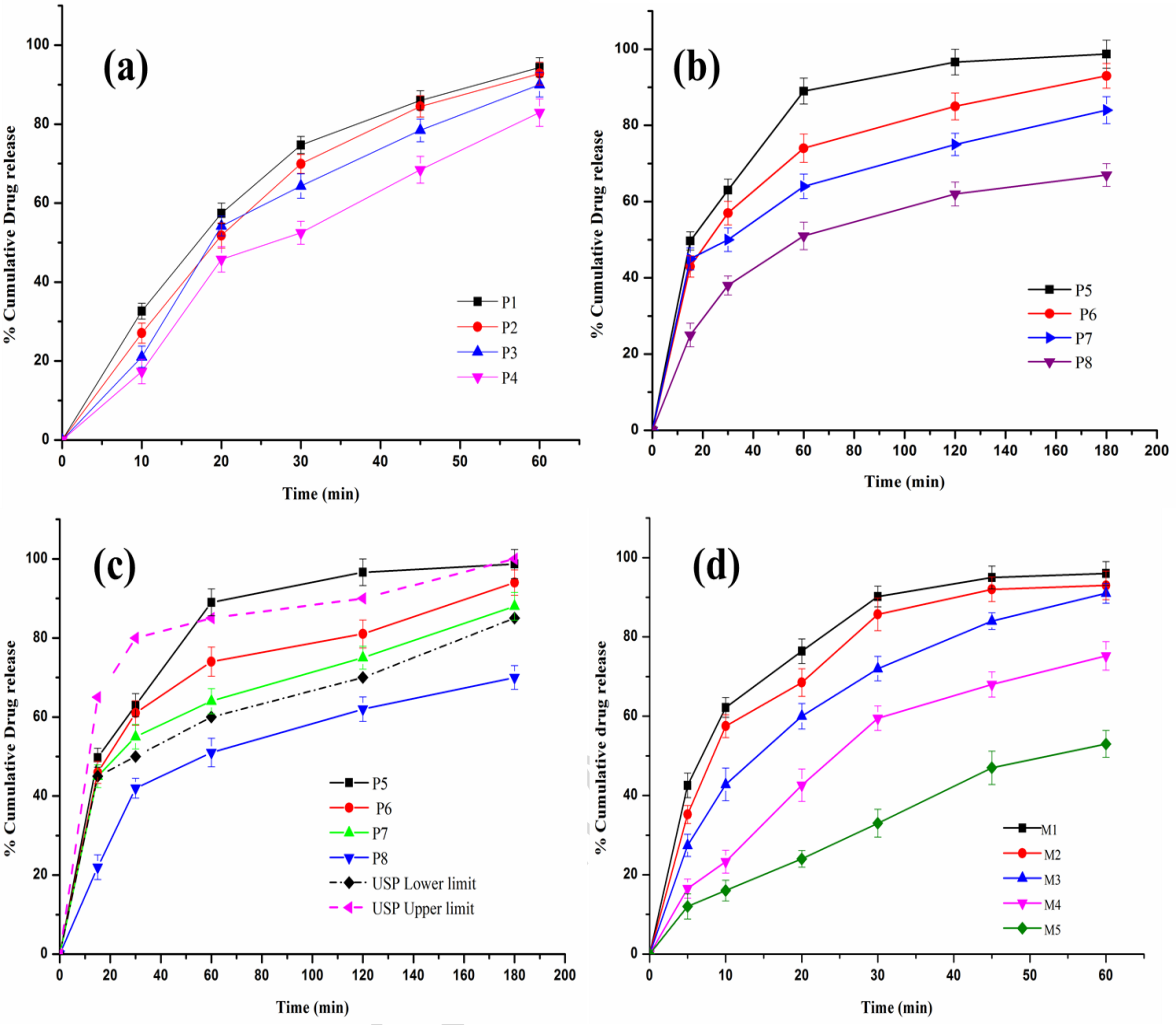

Fig. 10. In vitro, drug release pattern of (a) PML batches P1 to P4 in pH 5.8 PBS, (b) PML batches P5 to P8 in pH 5.8 PBS, (c) PML batches P5 to P8 in SGF, (d) MTF batches M1 to M5 in pH 6.8 PBS. Mean values ± S.D. (n=3).

3.7. Scanning electron microscopy

The scanning electron microscopy was used to examine the surface morphology of APIs and extrudates. The SEM micrographs of Soluplus® (Fig.11a, b, c) showed spherically shaped particles free from agglomeration with a rough and porous surface. The SEM micrographs of plain drugs (Fig. 11d and g) showed different crystalline shapes (PML showed rod and rectangular shaped particles while MTF exhibited spherical and oval shaped particles) without agglomeration. However, the morphological analysis of extruded granules (Fig. 11e and h) demonstrated the agglomerated microstructure and surface topography of these extruded

granules. Figure 11f and i showed a rough surface with a porous network with void spaces. The void spaces (between the agglomerated drug/polymer particles) on the surface of extrudates will lead to better compression and provide sufficient space for the binding/hardness to the compacts or tablet. On the basis of morphological and topographical examination, it can be concluded that ME of PML and MTF with Soluplus® may produce well-extruded granules along with excellent compatibility and binding efficiency.

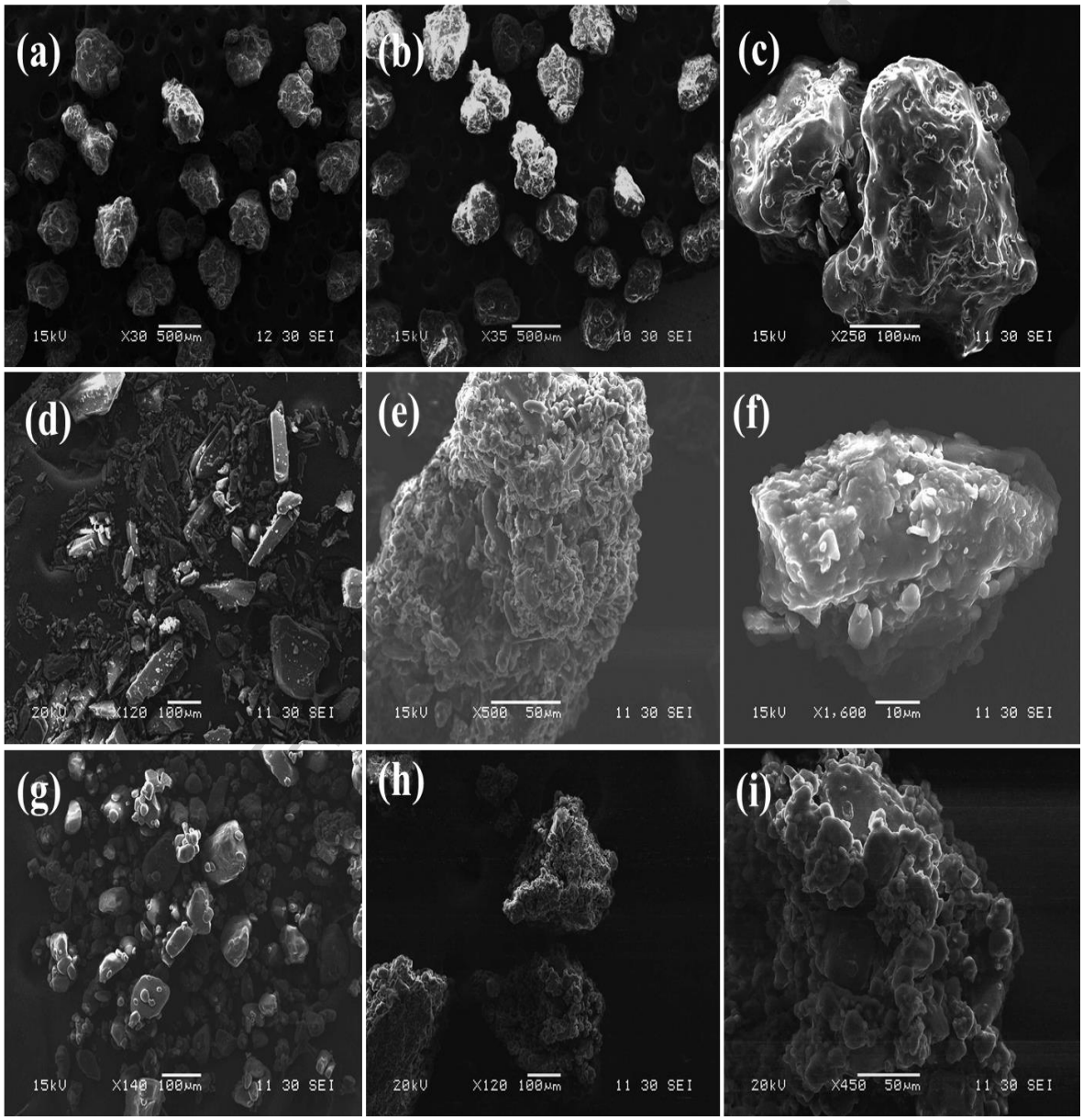

Fig. 11. Scanning electron micrograph of (a, b and c) plain Soluplus® at 30X, 35X and 250X, respectively, (d) plain PML, (e and f) PML extrudates at 500X and 1600X, respectively, (g) plain MTF, (h and i) MTF extrudates at 120X and 450X, respectively.

3.8. Thermo gravimetric analysis

The thermal stability of APIs polymer and extruded batches were evaluated by using thermogravimetric analysis. It is crucial to examine the thermal behavior of pure drug and excipients used in the formulation prior to the hot melt extrusion process to determine the maximum processing temperature. The TGA patterns of plain APIs (PML and MTF), Soluplus®, a physical mixture of the drug with Soluplus® and extruded batches prepared at various temperatures are shown in Fig. 12. The studies revealed that the formulation composition did not exhibit any weight loss at operating temperature during melt extrusion (ME) process. PML, MTF, corresponding physical mixture and extruded batches (operated at 70-130°C in HME) did not show any weight loss up to 250°C. This indicates that processing temperature selected was suitable for all material during ME process. TGA study outlined an optimum experimental window and the operating temperature range along with the indication of the thermal stability.

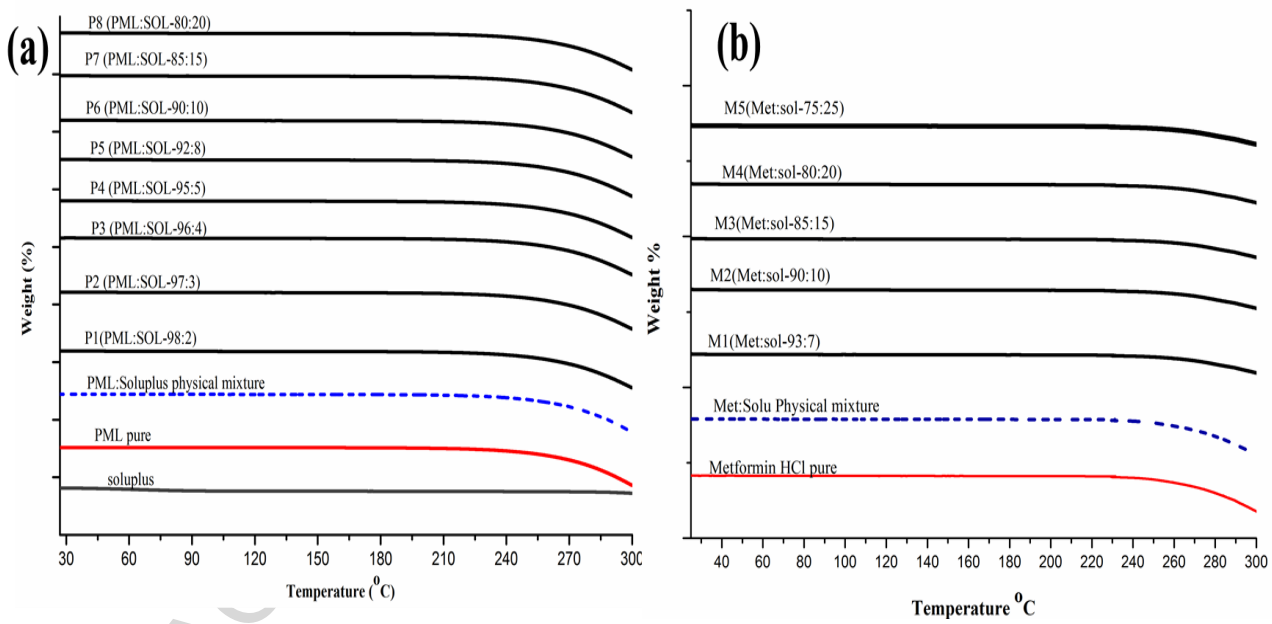

Fig. 12. TGA of (a) plain PML, Soluplus®, physical mixture and extruded batches, (b) plain MTF, Soluplus, physical mixture and extruded batches.

4. Conclusion

This work demonstrated that processing and formulation parameters had a significant effect on the extrudability and release pattern of the selected hydrophilic drugs. The rheological evaluation of polymer with different drug ratio helped in the analysis of viscoelastic properties of Soluplus® at various temperatures, which was correlated with torque parameter during the hot melt extrusion process. These results helped in the selection of suitable temperature range with desired viscosity and achieved the desired drug-polymer miscibility at operating temperature. This work showed that Soluplus® exhibited the melt binding efficiency with PML and MTF and can be used as a meltable binder via a hot melt extrusion process. In some of the batches (P1 and P2) as little amount of polymer as only 2-3% w/w Soluplus® was used for melt granulation and yet the compact-ability of granules and hardness of tablets were acceptable. This indicates not only the melt binding of Soluplus® at minimum concentration but also the superiority of melt granulation (HME) process over wet granulation. The extrudability and compact-ability of these drugs increase with an increase in Soluplus® concentration which ultimately influences the release pattern of these drugs from the extruded formulations. The delay in the release rate with the increase in Soluplus® content happened due to the gelling of the tablet in dissolution media which decelerate the erosion. This finding may be useful for the development of high dose immediate or modified release formulation with a continuous process, and high drug loading. The reduction in excipients content will also lead to a reduction of the tablet size and formulation cost and thus improves patient compliance.

Conflict of interest

The authors declare no conflict of interest.

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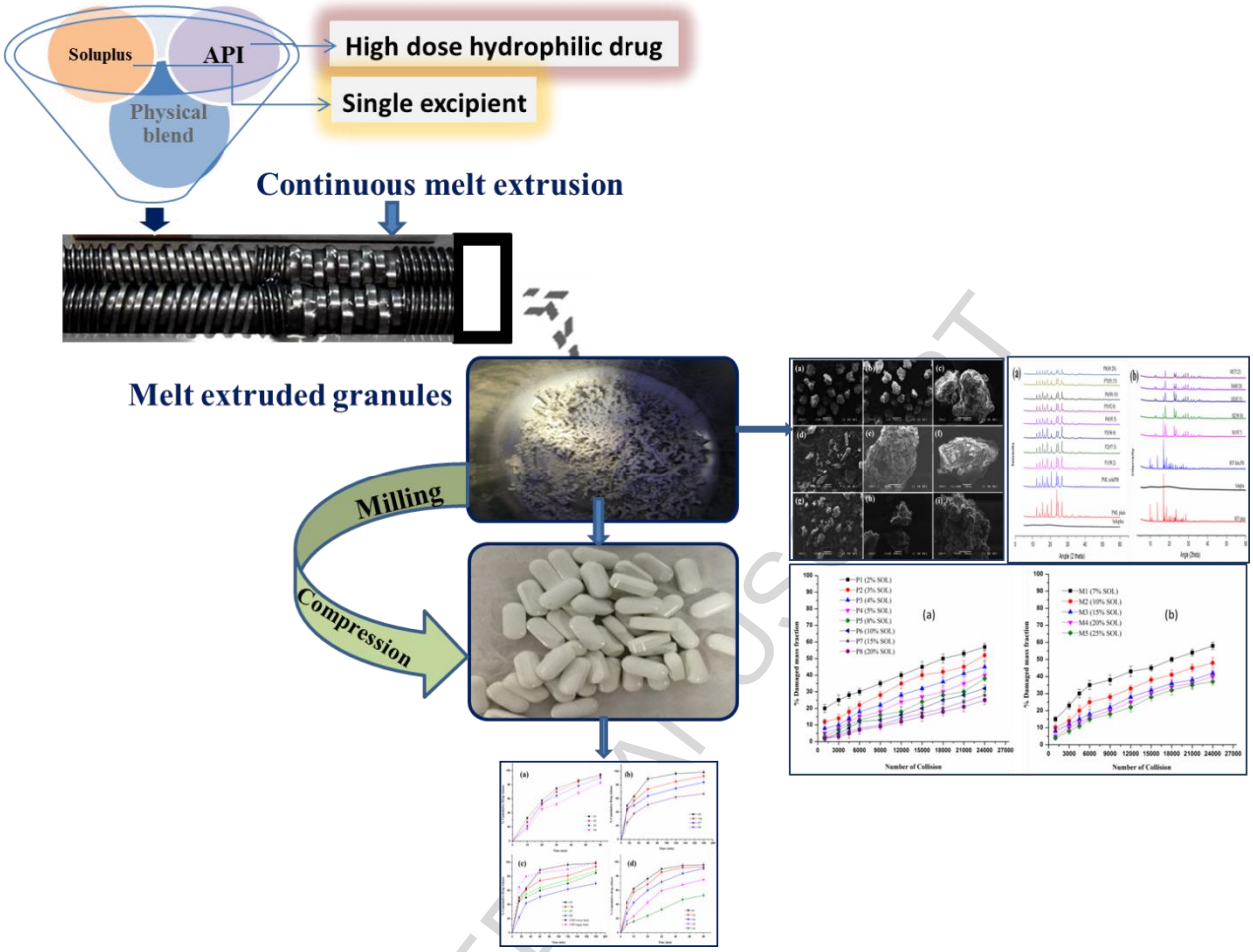

Graphical abstract

Highlights:

- Soluplus® has been introduced as a meltable binder for different APIs by using hot melt extrusion technology.
- Drying and milling of obtained extrude/granules are not required in this process.
- Melt binding property of Soluplus® played an important role in modifying the release pattern of APIs.
- Single excipient (Soluplus®) in minimum ratio caused reduced tablet size thereby improved patient compliance.
- Development of high dose conventional or novel formulation with continuous process.